The Unhealthy Parathyroid—Calcium Disorders

Introduction

This lesson focuses on the defects of the parathyroid gland and its pathway with specific attention paid to the diseases that affect **calcium**. It does not cover any other acquired or congenital form of bone disease. This distinction is arbitrary, as bone disease, calcium, and parathyroid hormone (PTH) are intimately interrelated. But in order to sustain focus on the mechanisms of disease and their treatment, we have isolated the conditions that relate to calcium dysregulation to this lesson and placed it after the lesson on PTH, which regulates and is regulated by calcium. Separately, we discuss normal bone physiology, and only after *that* lesson do we round out the other bone disorders. You'll notice they are all part of the same series—study them together. There is too much content to put them into one lesson, but you should yoke all four lessons together as one large lesson in your mind-brain.

We cover the symptoms of hypercalcemia and hypocalcemia, then discuss the effects of excess PTH in general, before closing with the "calcium diseases."

Overview of the Players of Calcium

The details of these mechanisms are discussed in detail in Parathyroid #3: *Healthy Bone* and were discussed in Parathyroid #1: *The Healthy Parathyroid.* The information provided here is sufficient to comprehend the mechanisms that follow.

The **parathyroid gland** produces **parathyroid hormone** by default. With no signaling, PTH is released. Each parathyroid gland cell expresses a **calcium-sensing receptor** (CaSR). Stimulation of the CaSR by rising calcium levels activates both G_i and G_q. G_i inhibits the **AC-cAMP-PKA** second messenger system, decreasing cAMP levels and PKA activity. G_q stimulates the **G_q-IP_3-DAG** second messenger system. Rising cytoplasmic calcium inhibits proliferation, synthesis of PTH, and release of PTH. Use an extreme amount of caution. In every cell type we have ever taught you—myocyte, nerve terminal, endocrine cell, etc.—increasing the cytoplasmic calcium is a stimulatory signal, making the cell do whatever it does more or better. In the cells of the parathyroid gland, increased serum calcium results in increased cytoplasmic serum and **inhibition** of the cell.

PTH stimulates the **PTH receptor** on **osteoblasts**, the tubular cells of the **PCT** (proximal convoluted tubule), and the tubular cells of the **DCT** (distal convoluted tubule). In the kidney, PTH results in the **elimination of phosphate** and **reabsorption of calcium**. In the kidney, PTH also results in the synthesis of 1,25-vitamin D, which increases calcium and phosphate absorption from the gut. PTH results in the clearing of bone, increasing the calcium and phosphate in the blood, but at the cost of enhanced **bone clearing** by **osteoclasts**. "*The kidney always wins,*" so the net effect of PTH is to increase serum calcium and decrease serum phosphate.

Osteoblasts are stimulated by the PTH receptor to express **RANK ligand (RANK-L)** and **IL-6**. These soluble chemokines activate **RANK** and the **IL-6 receptor** on osteoclasts. Activation of these receptors in bone marrow results in the **differentiation and maturation** of osteoclasts into mature osteoclasts. Activation of these same receptors on mature osteoclasts in bone induces the resorption of bone. Osteoclasts clear bone, but only when told to by osteoblasts, and then only when osteoblasts are told to by PTH. Osteoblasts also make **osteoprotegerin** (OPG). OPG is a RANK-L decoy receptor. The presence of OPG limits the effects of RANK-L. Osteoblast PTH receptor activation **decreases the expression of OPG** at the same time as it increases RANK-L and IL-6 expression. PTH receptor activation also stimulates osteoblasts to produce **alkaline phosphatase** as they build bone. Osteoblasts build bone.

You did read all that correctly. The PTH signal directly stimulates osteoblasts to build bone, while the PTH signal indirectly stimulates osteoclasts to clear bone. Bone remodeling requires both osteoclast activity and osteoblast activity at the same time. PTH drives both—directly in osteoblasts and indirectly in osteoclasts—but tips the scale towards bone clearing.

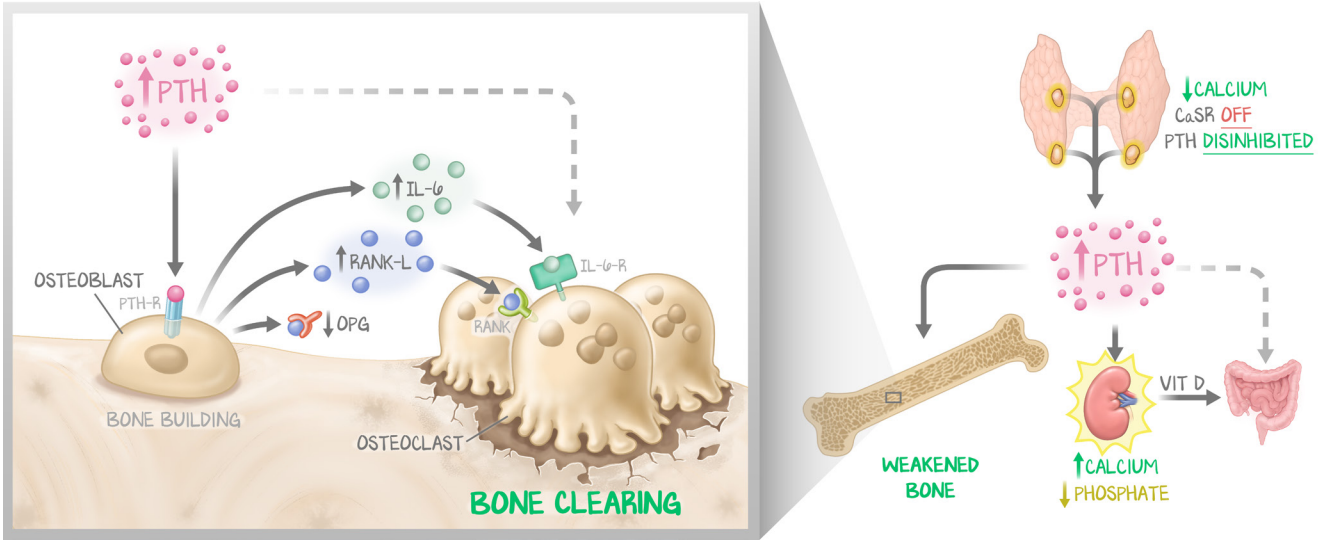

Figure 2.1: Overview of Calcium Dysregulation
PTH increases calcium, reduces phosphate, increases vitamin D, and clears bone. Although PTH receptor activation on osteoblasts does stimulate osteoblasts to build bone, PTH receptor activation also stimulates those osteoblasts to stimulate osteoclasts, which clear bone. The net effect is more clearing than building. For this lesson, PTH clears bone. The details (such as those molecules used to communicate the PTH receptor signal from osteoblast to osteoclast) come in the lessons on bone that follow this one.

Symptoms of PTH Excess

Unrelated to the variation in calcium and phosphate are PTH's effects on bone and the kidney. You're going to learn more about bone in the coming lessons. We know you aren't familiar with the nomenclature and histology of bone yet, but the associations between PTH and bone resorption are so crucial that we're going to give you a preview of the coming lessons in order for you to hear it and see it from the perspective of PTH. Don't freak out over how technical the next paragraphs will be. Let it soak in, do the remainder of the parathyroid lessons, then come back here.

Symptomatic, untreated primary hyperparathyroidism manifests with three interrelated skeletal abnormalities: osteopenia, brown tumors, and osteitis fibrosa cystica. **Osteopenia** results from increased osteoclast activity that clears more bone than osteoblasts can create. The increased osteoclast activity in hyperparathyroidism affects cortical bone (**subperiosteal** and **endosteal** surfaces) more severely than the trabecular bone.

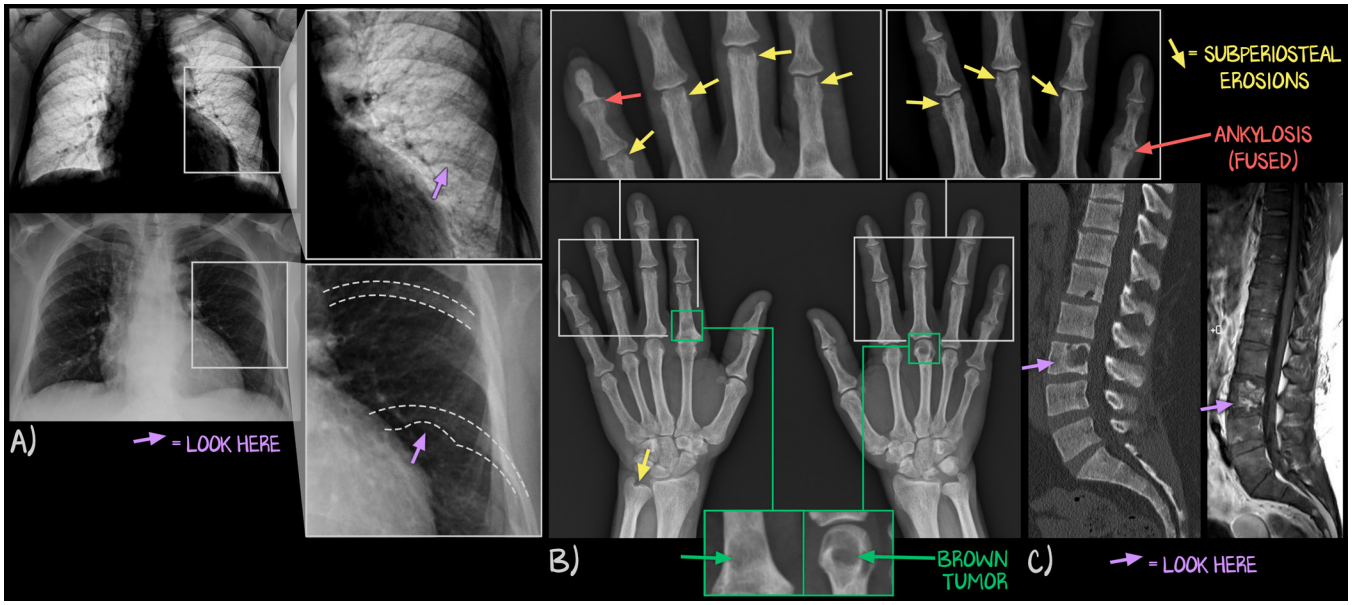

Figure 2.2: Radiographic Osteitis Fibrosa Cystica
(a) Color-inverted (black/white) chest X-ray demonstrating rib notching, periosteal erosions in a rib. (b) Multiple changes are noted in the hands bilaterally, including multiple subperiosteal erosions, ankylosis, and brown tumors. (c) Sagittal CT (bone window) showing large periosteal erosions that were also found on T1-weighted MRI. These are brown tumors.

However, there is more exposed surface area in trabecular bone, so osteoclasts tunnel into and centrally dissect the length of the trabeculae, creating the appearance of railroad tracks and producing what is known as dissecting osteitis. The marrow spaces around the affected surfaces are replaced with fibrovascular tissue. As bone is cleared away, as bone mass decreases, affected patients are increasingly susceptible to fractures, bone deformation, and joint problems. Overactivation of osteoclasts clears the bone, and the bone loss predisposes to microfractures and secondary hemorrhages. This results in acute inflammation (neutrophils, macrophages, then fibroblasts). After many repeated bouts, with many simultaneous microfoci of granulation tissue, the gross appearance of a **brown tumor** is seen. The color results from the vascularity of granulation tissue admixed with bone, bone marrow, and leukocytes. Because osteoclasts are put into overdrive, multinucleated giant cells will be present, giving this the histological appearance of an osteoclastoma (Parathyroid #5: *Bone Tumors*). The combination of increased bone cell activity (leading to osteopenia), peritrabecular fibrosis of bone marrow, and cystic brown tumors within bone is called **osteitis fibrosa cystica**, which is rarely encountered because hyperparathyroidism is usually diagnosed on routine blood tests and treated at an early stage. Control of hyperparathyroidism allows the bony changes to regress or disappear completely.

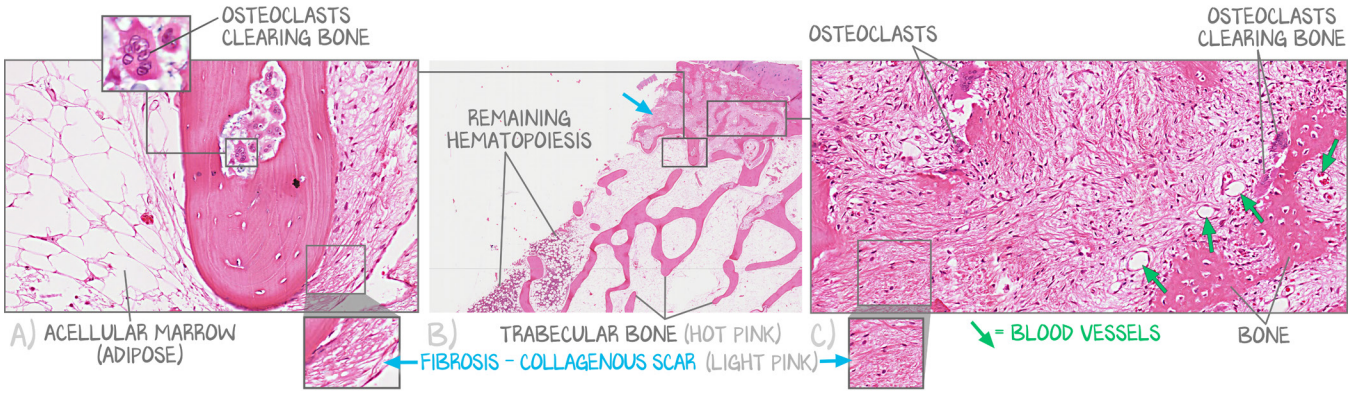

Figure 2.3: Histologic Osteitis Fibrosa Cystica
These are three samples from the same tissue, each captured at a different magnification. The low-powered view in (b) demonstrates the paucity of bone and hematopoiesis. Trabeculae (solid pink) run through an acellular marrow, the marrow replaced by fat (adipose is white). What little remaining areas of hematopoiesis are left (lower left) pales in comparison to the adipose. There is even more fibrosis of the marrow (upper right) than hematopoiesis. The magnification in (a) shows osteoclasts in a resorption canal, clearing bone perpendicularly to the image plane, giving the appearance they are encased in the bone. There is also a high-powered view of the hyperparathyroidism-associated fibrosis and the acellularity of the marrow (associated with many conditions) to the left. The magnification in (c) was chosen to demonstrate how little bone there is, how many osteoclasts are active, and how all that's left behind are the swirling pink fibroblasts, the collagen they deposit, and the many small blood vessels those fibroblasts use to fuel the process of scarring.

It wasn't worth it to try to clean that up and avoid technical jargon. The signal for osteoclast activity is from the osteoblasts, not PTH. PTH receptor activation also stimulates osteoblasts' building of bone. Just as the bone is constantly remodeled, osteoclast activity is tied to osteoblast activity—the clasts clear the bone so osteoblasts can rebuild the lamellar bone. **Alkaline phosphatase** is an enzyme that osteoblasts secrete into their immediate surroundings to facilitate the ossification of osteoid, the addition of calcium and phosphate into the crystals that give bone its strength. Therefore, with increased PTH, one laboratory finding in the blood is **elevated alkaline phosphatase**.

By preventing the reabsorption of phosphate by the PCT, there is an increase in phosphate in the urine. By reabsorbing calcium from the DCT, you would expect less calcium to end up in the urine. But because there is a higher circulating concentration of calcium, more calcium is filtered. Thus, high PTH both causes the serum calcium to be high and predisposes the patient to **calcium phosphate stones**. These stones are related to PTH and not hypercalcemia.

The abnormalities most directly related to hyperparathyroidism are bone disease and calcium phosphate stones (see next section), whereas those attributable to hypercalcemia include nephrolithiasis (calcium oxalate stones), fatigue, weakness, pancreatitis, metastatic calcifications, and constipation.

Symptoms of Hypercalcemia

The classic presentation of hypercalcemia is "bones, stones, abdominal groans, and psychic moans." These symptoms are independent of why the calcium level is high. Specifically, they are unrelated to PTH levels.

"Bones" refers to **bone pain** and is usually secondary to fractures in weakened bone or induced by the cause of hypercalcemia. That is, the reason the calcium level is high is also usually the reason for bone pain. The high calcium doesn't cause the pain; the cause of the hypercalcemia causes the pain by demineralizing the bone. "Stones" refers to **nephrolithiasis**. With high circulating calcium, more calcium is filtered. This provokes **hypercalciuria** and, therefore, an increased risk for the formation of **calcium oxalate stones**. Hypercalcemia alone increases the risk of calcium oxalate stones; hypercalcemia

caused by elevations in PTH increases the risk of calcium phosphate stones. "Abdominal groans" is to relay the gastrointestinal disturbances, including **constipation**, nausea, **peptic ulcers**, gallstones, and **pancreatitis**. "Psychic moans" refer to the central nervous system effects, namely **encephalopathy, coma,** and **seizures**.

Most patients with hyperparathyroidism as the cause of their hypercalcemia will have **asymptomatic elevations in calcium**, and PTH symptoms will predominate. Most patients who have symptomatic hypercalcemia producing the "stones, bones, abdominal groans, and psychic moans" will have a very elevated calcium level, and the cause of that hypercalcemia will be a **malignancy**.

SYMPTOMS OF PTH	SYMPTOMS OF HYPERCALCEMIA
Bone pain = osteitis fibrosa cystica Osteopenia Fractures	Bone pain, usually from the cause of hypercalcemia
Stones—nephrolithiasis = Calcium phosphate	Stones—nephrolithiasis = Calcium oxalate
↑ Alkaline phosphatase	Abdominal groans—Pancreatitis, constipation, nausea, peptic ulcers
	Psychic moans—encephalopathy, seizure

Table 2.1: Symptoms of PTH and Ca

Overview of Disease

PTH-dependent hypercalcemia is caused by hyperparathyroidism. Hyperparathyroidism comes in three forms: primary, secondary, and tertiary. Primary hyperparathyroidism tends to cause mild asymptomatic hypercalcemia found on routine screening of serum chemistries and is from a functioning adenoma of one gland. Secondary hyperparathyroidism is an appropriate elevation in PTH in order to sustain a normal calcium level. Most commonly, this is from vitamin D deficiency secondary to chronic kidney disease. Tertiary hyperparathyroidism is caused by ongoing secondary hyperparathyroidism that isn't treated, the loss of calcium inhibition resulting in proliferations that acquire mutations. Tertiary is just like primary, except tertiary has had secondary happen first.

Hypercalcemia independent of PTH and the parathyroid glands takes two main forms—cancer and other lower-yield stuff. "Cancer" (nebulously defined and of multiple types) can either make parathyroid hormone-related peptide (PTHrP) or metastasize to bone. In either case, the calcium level tends to get very high. Hypercalcemia of other low-yield stuff is in the form of immobilization or excess vitamin D. Excess vitamin D can be due to toxic ingestion (ingesting too much vitamin D in the diet) or a granulomatous disease, like TB or sarcoid. Granulomas can convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D independently of the PTH signal.

Hypoparathyroidism leads to symptomatic hypocalcemia. Symptomatic hypocalcemia is essentially always caused by hypoparathyroidism. We will discuss hypocalcemia in its own section later.

HYPERCALCEMIA		HYPOCALCEMIA
PTH Dependent	PTH Independent	
Hyperparathyroidism 1. Primary (adenoma > hyperplasia) 2. Secondary 3. Tertiary	Hypercalcemia of malignancy 1. PTHrP 2. Lytic lesions	Surgical removal
Familial hypocalciuric hypercalcemia	Vitamin D toxicity	DiGeorge syndrome
	Granulomatous Disease	
	Immobilization	

Table 2.2: Causes of Calcium Dysfunction

Primary Hyperparathyroidism

A primary endocrine disease is caused by the endocrine gland itself. Hyperparathyroidism is caused by excess secretion of PTH by the parathyroid gland. There are four parathyroid glands. In primary hyperparathyroidism, a single cell in one of those four glands gains the ability to proliferate and produce PTH inappropriately. This causes calcium to rise. All other cells have a functioning CaSR and no mutation that promotes proliferation or the unregulated production of PTH. Thus, in primary hyperparathyroidism, **one gland is hyperfunctioning,** and **all other glands are silenced.**

Even though hyperparathyroidism is a common endocrine disorder and one of the most common causes of asymptomatic hypercalcemia, the underlying genetic mechanisms have not been well elucidated. Most endocrine glands function by being stimulated; the activation of a receptor leads to a feedforward signal to produce the hormone or proliferate. Similar to the lactotropes of the anterior pituitary, in which dopamine from the hypothalamus is inhibitory, and the absence of dopamine results in disinhibition and the release of prolactin, the parathyroid gland is under negative inhibitory control by calcium. If the calcium goes up, the CaSR is activated, G_i-AC-cAMP-PKA is turned on (inhibiting the adenylyl cyclase second messenger system), and G_q-IP_3-DAG is turned on (inhibiting the release of PTH). Therefore, mutations that lead to overactivity are not going to be from gain-of-function mutations in these pathways. Instead, the mutations we know of are completely unrelated to the CaSR pathway.

Forty percent of parathyroid adenomas express increased **cyclin D1**, a cell-cycle checkpoint cyclin. Cyclin D1 is the final molecule expressed in the G_1/S checkpoint. Cyclin-dependent kinases are expressed constitutively. Increased cyclin expression is all that is required to activate the CDK and move through the checkpoint (Inflammation and Neoplasia #5: *Cell Cycle*). Twenty percent of pituitary adenomas have a pericentromeric **inversion** of chromosome 11 (location of both cyclin D1 and the gene for PTH). This inversion places the cyclin D1 gene under the control of the PTH's promoter. PTH is made more frequently than cyclin D1. But now that cyclin D1 is under the control of PTH's promoter, increased expression of cyclin D1 hijacks control of the cell cycle and induces overproliferation. Thirty percent of parathyroid adenomas have mutations in both copies of the **MEN1** gene, also on chromosome 11. These sporadic parathyroid adenomas have the same behavior and genetic mutations seen in the familial MEN1 syndrome. The only difference is that the sporadic adenoma is a monoclonal expansion of one cell that develops a somatic mutation—all other cells in the parathyroid gland have intact MEN1 genes.

Primary hyperparathyroidism is commonly diagnosed by **asymptomatic, routine blood work** that reveals a **mildly elevated calcium**. Because the parathyroid adenoma is autonomously secreting PTH, the **calcium is high because the PTH is high**. Because PTH is high and "the kidney always wins," the **phosphate will be low**.

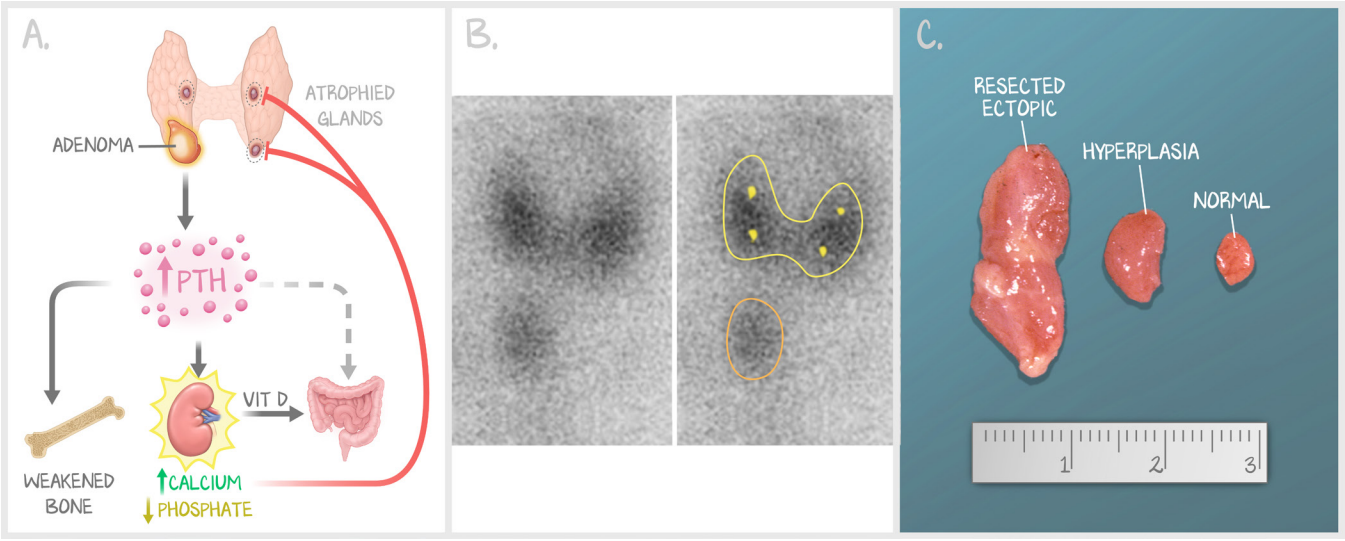

Figure 2.4: Primary Hyperparathyroidism
(a) A schematic of primary hyperparathyroidism. Excess PTH leads to weakened bone and hypercalcemia. Hypercalcemia silences normal parathyroid glands, which atrophy. (b) Sestamibi scan demonstrating an intense signal from an ectopic focus with normal activity of the parathyroid glands (the parathyroid glands are perceived by the scan to conform to the shape of the thyroid gland). Although atrophic, the other glands need not be entirely silent. (c) Three parathyroid glands (not from the same patient, as normal or atrophic glands should not be resected with an ectopic focus as they will recover normal function) demonstrating an enlarged ectopic adenoma (very large), increased size due to hyperplasia (not unregulated proliferation, but rather as seen in secondary hyperparathyroidism), and normal.

Parathyroid adenomas are almost always solitary and, similar to the normal parathyroid glands, may lie near the thyroid gland or in an ectopic site (e.g., the mediastinum). The typical parathyroid adenoma averages .5–5 g (the weight of a normal parathyroid gland is approximately 1 g) and consists of a well-circumscribed, soft, tan to reddish-brown nodule enclosed by a delicate capsule. The other glands outside the adenoma are usually normal in size or somewhat shrunken due to feedback inhibition by elevated serum calcium levels. **Surgical resection** of the adenoma is curative. In fewer than 1% of cases is the adenoma a carcinoma. Immediately upon removing a hyperfunctioning adenoma, the remaining parathyroid glands need a chance to catch back up. Usually, the parathyroid glands recover within 24 hours. However, there may also be signs of hypocalcemia the morning after surgery, as discussed below.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is caused by any condition that gives rise to chronic hypocalcemia, which leads to compensatory overactivity of the parathyroid glands. **Chronic kidney disease** is by far the most common cause of secondary hyperparathyroidism. CKD causes two problems. First, with reduced elimination of phosphate, phosphate levels rise, phosphate binds with free calcium in the blood and causes **relative hypocalcemia**. Although the total calcium may be normal, the ionized calcium is reduced, bound to phosphate, and it is ionized calcium the CaSR responds to. Second, **reduced synthesis of 1,25-vitamin D** reduces the absorption of calcium from the gut. This is likely the primary mechanism of secondary hyperparathyroidism, as secondary hyperparathyroidism is also seen in conditions of **fat malabsorption** (vitamin D is a fat-soluble compound) and other causes of **vitamin D deficiency**.

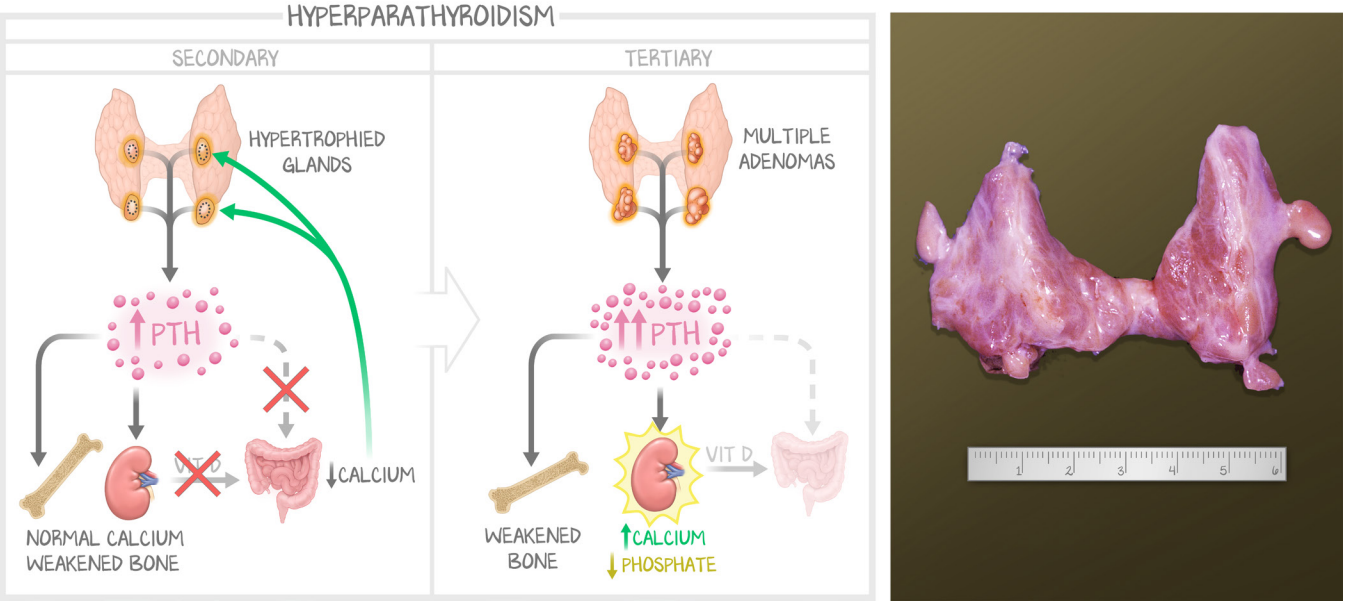

Figure 2.5: Secondary and Tertiary Hyperparathyroidism
In secondary hyperparathyroidism, vitamin D deficiency due to chronic kidney disease initiates the pathology. Not enough calcium or phosphate is absorbed by the gut. The low calcium level disinhibits the parathyroid glands, which make more PTH. PTH, in turn, extracts calcium from the bone and reabsorbs more filtered calcium from the kidneys. The net effect is to sustain calcium levels near normal, but at the cost of bone and a chronic, albeit mild, disinhibition of the parathyroid glands. Disinhibition also results in proliferation. The gross section demonstrates a normal thyroid and hyperplasia of all four parathyroid glands. The parathyroid glands should be less than 5 mm in diameter and never greater than 1 cm. An equal increase in all four glands without the presence of a mass indicates secondary hyperparathyroidism. Sustained long enough, those parathyroid glands accumulate mutations that make them autonomous. Tertiary hyperparathyroidism presents just like primary, only with many hot nodules on sestamibi instead of just one. Tertiary hyperparathyroidism can be prevented by treating secondary hyperparathyroidism with what is deficient—calcium, phosphate, and vitamin D—orally.

All four parathyroid glands in secondary hyperparathyroidism are **hyperplastic**. They proliferate whenever the CaSR is off. They produce PTH whenever the CaSR is off. In secondary hyperparathyroidism, the chronically low levels of calcium turn off all CaSRs equally. However, as in primary hyperparathyroidism, the degree of glandular enlargement is not necessarily symmetric. Microscopically, the hyperplastic glands contain an increased number of chief cells.

As chronic kidney disease progresses towards end-stage renal disease, phosphate accumulation can cause the precipitation of calcium into tissues. The vascular calcification associated with secondary hyperparathyroidism may occasionally result in significant ischemic damage to the skin and other organs, a process called **calciphylaxis**. Calciphylaxis occurs when the **calcium/phosphate product is greater than 55** (multiply the total calcium by the total phosphate). Patients with chronic kidney disease are prophylactically placed on **vitamin D supplementation** to avoid secondary hyperparathyroidism. **Phosphate binders** (sevelamer) are used to drive the phosphate levels down. **Calcimimetics** (cinacalcet) stimulate the CaSR receptors to limit PTH release. You need only be able to recognize these medications as chronic kidney disease medications.

Tertiary Hyperparathyroidism

In a minority of patients, secondary hyperparathyroidism progresses to tertiary. The chronically low calcium disinhibits the proliferation of chief cells in the parathyroid gland. That's why the glands get bigger in the first place. With proliferations come opportunities for new mutations. Tertiary hyperparathyroidism is just like primary, except that the driver of hyperparathyroidism was a mutation accumulated during the period of secondary hyperparathyroidism. Therefore, there are often **multiple autonomous adenomas** in **more than one gland.** In tertiary hyperparathyroidism, there will also be a **history of secondary hyperparathyroidism** and almost always a history of chronic kidney disease. In primary, there will be a single adenoma and no history of secondary hyperparathyroidism or CKD.

Hypercalcemia of Malignancy

Among other causes of hypercalcemia, malignancy stands out as the **most frequent cause of** symptomatic **hypercalcemia** in adults. The most common mechanism (in ~80% of cases) through which osteolytic tumors induce hypercalcemia is the secretion of **PTH-related peptide (PTHrP)**, which has functions similar to those of PTH in inducing osteoclastic bone resorption and hypercalcemia. PTHrP does the same thing as PTH, but PTHrP is produced by a cancer without any CaSR to inhibit it. As the calcium goes quite high, the normal parathyroid glands completely stop making PTH (the appropriate response to rising calcium levels). Blood tests for PTH do not identify PTHrP, and so, if you suspect a PTHrP-producing cancer, a PTHrP test must be ordered specifically. The remaining 20% induce hypercalcemia through metastases to the bone.

One special variant is multiple myeloma (Hematology Oncology: Proliferation #5: *Plasma Cell Dyscrasias*). The myeloma plasma cell tricks the osteoblasts into releasing the cytokines that osteoblasts normally produce when stimulated by PTH. The myeloma cells secrete MIP1α, which in turn increases stromal cell release of RANK-L. The cancer is in the bone and inducing osteoclasts to clear bone. It isn't a metastasis, and it isn't PTH driven.

Treating symptomatic hypercalcemia. Because hypercalcemia due to malignancy can reach very high calcium levels, it is the most likely thing to cause the stones, bones, groans, and moans. Treating it involves getting the calcium levels down. The first and most important treatment is **fluid resuscitation**. This dilutes the calcium in the plasma by expanding the plasma volume and facilitates urinary excretion of calcium. The treatment for symptomatic hypocalcemia is fluids, fluids, fluids, fluids, fluids, and some medications. **Calcitonin** can be used to temporize the hypercalcemia. Its duration of effect is short, and its overall impact on calcium levels minimal. It is given subcutaneously and as an adjunct to other, better treatments. **Bisphosphonates** (discussed in the lessons on bone disorders) are given **intravenously** in the acute setting. These take days to work but will eventually slow down the osteoclasts. **The treatment for symptomatic hypercalcemia is fluid resuscitation**.

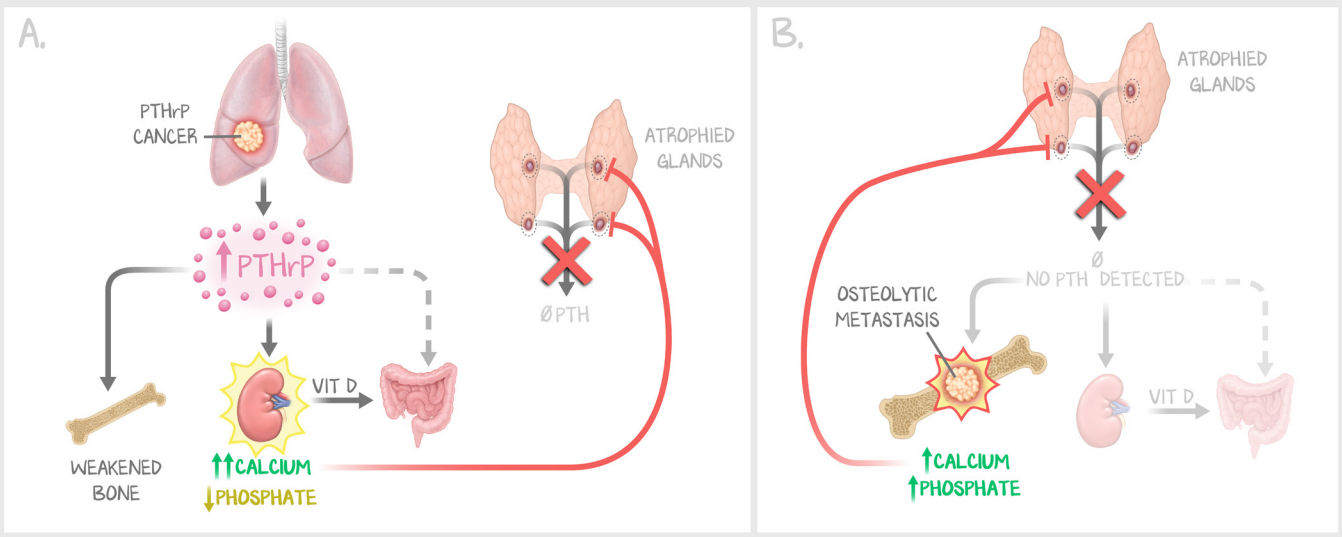

Figure 2.6: Hypercalcemia of Malignancy
(a) Some cancers not in bone release PTHrP, which acts just like PTH. This excess PTHrP signal causes a primary hyperparathyroidism-like picture but with much higher calcium. The calcium is high, and the phosphate is low. Hypercalcemia silences the parathyroid glands, and so the PTH is undetectable. But PTHrP is elevated, driving the pathology. (b) In lytic lesions metastasized to bone, the cancer is in the bone, eating the bone, and releasing calcium and phosphate. There are high calcium and high phosphate levels. Hypercalcemia silences the parathyroid glands, as did the PTHrP cancer, but because there is no PTH or PTHrP signal, the kidney cannot win, and so the calcium and phosphate levels are both high. The difference between them is the elevated phosphate level and absent PTHrP.

If anyone ever tells you to give diuretics to treat hypercalcemia, politely tell them they are a decade (or two) behind the times. For the entirety of the 2010s, we had to undo the teaching that loop diuretics help hypercalcemia. They do not. They concentrate the blood and make symptoms worse. You, who likely have not been taught that loop diuretics treat calcium, may find this paragraph odd. But medical science learned from its mistakes, and those mistakes are equally as important as our successes. **No diuretics to treat calcium.**

Hypocalcemia

The hallmark of hypocalcemia is tetany, which is characterized by neuromuscular irritability resulting from decreased serum calcium levels. The symptoms range from circumoral numbness or paresthesia (tingling) of the distal extremities and carpopedal spasm to life-threatening laryngospasm and generalized seizures. The classic findings on physical examination are Chvostek's sign and Trousseau's sign. Chvostek's sign is elicited in subclinical disease by tapping along the course of the facial nerve, which induces contractions of the muscles of the eye, mouth, or nose. Trousseau's sign refers to carpal spasms produced by the occlusion of the circulation to the forearm and hand with a blood pressure cuff for several minutes. A low calcium level can be treated with calcium supplementation. Absence of the parathyroid gland results in need for aggressive calcium, phosphate, and vitamin D supplementation.

You should consider **hypocalcemia** and **hypoparathyroidism** as the same condition.

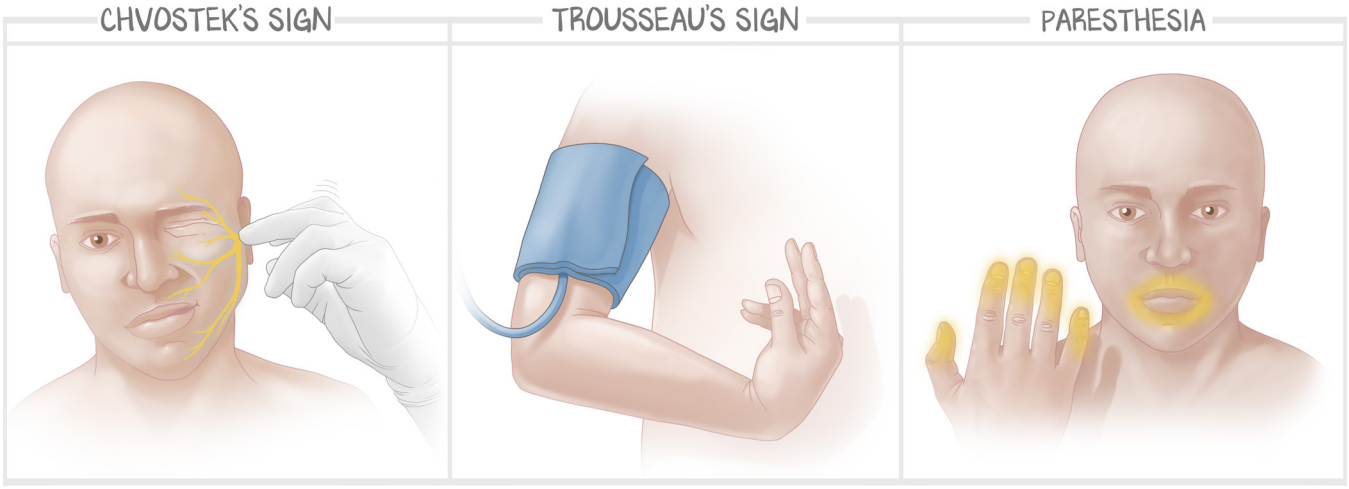

Figure 2.7: Hypocalcemia Symptoms
(a) Chvostek's sign is when tapping the facial nerve over the parotid results in both an exaggerated spasm (hyperreflexia) and the inability to extinguish the reflex (normal patients may demonstrate the reflex once, but not on future taps). (b) Trousseau's sign is a carpopedal spasm associated with blood pressure cuff inflation. c) Distal finger paresthesia and perioral paresthesia are another sign of hypocalcemia.

Surgically induced hypoparathyroidism occurs with the inadvertent removal of all the parathyroid glands during thyroidectomy or removal of too large a proportion of parathyroid tissue in the treatment of primary hyperparathyroidism. When the patient first comes out of the parathyroidectomy, even when there are glands left behind, if the gland removed was hyperfunctioning, the others may need time to catch up. Ionized serum calcium levels can be tracked following surgery to anticipate the need for treatment. A PTH level at the end of the day of surgery predicts calcium the next morning. If there is **symptomatic hypocalcemia**, treat with IV calcium gluconate. Because there was a need for IV calcium gluconate, the patient is placed on **calcium and vitamin D** orally for several weeks (up to eight). An attempt to wean the patient assesses whether the parathyroid glands will recover.

Congenital absence of parathyroid glands can occur in conjunction with other malformations, such as thymic aplasia and cardiovascular defects, or as a component of 22q11.2 deletion syndrome. When thymic defects are also present, the condition is called **DiGeorge syndrome**. We covered DiGeorge syndrome in Immunology #15: *Immunodeficiency*.

Weird Low-Yield Stuff

Granulomas are known to convert 25-vitamin D into 1,25-vitamin D. Why or how doesn't matter. The patient will have high calcium and high phosphate, and their PTH will be low. The patient should have a history of sarcoidosis or tuberculosis (some reason to have a granuloma). One clinical clue is to suppress the granuloma (made of overactive macrophages) with **glucocorticoids**. A rapid reduction in the calcium following steroid administration is classic for the disease.

Familial hypocalciuric hypercalcemia is a condition caused by a loss-of-function mutation in the parathyroid **calcium-sensing receptor gene**, which results in decreased sensitivity to extracellular calcium. The setpoint for "normal calcium" is higher than usual. Thus, there is more PTH produced to keep the calcium slightly elevated. With more PTH, there is also lower urine calcium.

Pseudohypoparathyroidism is a condition in which the **DCT is unresponsive to PTH** stimulation. There is hypocalcemia despite having a high PTH level. This is also known by the eponym Albright hereditary osteodystrophy and presents with **shortened fourth and fifth digits** and short stature.